Image AF/1644

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application of:	Rittershaus et al.
Serial No.:	09/529,762
Filed:	April 18, 2000
Entitled:	XENOGENEIC CHOLESTERYL ESTER TRANSFER PROTEIN (CETP) FOR MODULATION OF CETP ACTIVITY

ON APPEAL

ART UNIT: 1644

EXAMINER: Huynh

Atty. Docket No.: TCS-420.1P US

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Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

TRANSMITTAL LETTER

Sir:

Transmitted herewith are: [X] Appellants' Reply Brief, in triplicate; and [X] a return receipt postcard for filing in the above-identified application.

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[X] The Commissioner is hereby authorized to charge payment of any additional fees required in connection with the paper(s) transmitted herewith, or to credit any overpayment of same, to Deposit Account No. 50-0268. A duplicate of this transmittal letter is transmitted herewith.

Respectfully submitted,

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CERTIFICATE OF MAILING

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Stephanie L. Leicht
Stephanie L. Leicht

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application of:	Rittershaus and Thomas	**ON APPEAL**
Serial No.:	09/529,762	
Filed:	April 18, 2000	ART UNIT: 1644
Entitled:	Xenogeneic Cholesteryl Ester Transfer Protein (CETP) for Modulation of CETP Activity	EXAMINER: Huynh

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REPLY BRIEF PURSUANT TO 37 C.F.R. §1.193(b)(1)

Sir:

Pursuant to 37 CFR § 1.193(b)(1), Appellants submit this Reply Brief in response to the Examiner's Answer, mailed January 2, 2004 in the above-identified case. This Reply Brief is made to address and correct statements made in the Examiner's Answer, which indicate a misapplication of the patent law, misinterpretation of the reference cited by the Examiner, and a misunderstanding of Appellants' invention as embodied in the claims on appeal.

Appellants are filing this Reply Brief in triplicate within two months of the Examiner's Answer. No fee is believed to be required with this paper, however, the Commissioner is authorized by the undersigned to charge any additional fees required in connection with this Reply Brief and the papers submitted herewith to PTO Deposit Account No. 50-0268.

Appellants confirm that the Real Party in Interest and the state of Related Appeals and Interferences as reported in the Appeal Brief (submitted October 14, 2003) remain the same.

The claims on appeal remain the same. Appellants have previously described the grouping of these claims on appeal (see, page 7 of the Appeal Brief).

Grouping of Claims

The Examiner has disputed Appellants' statements regarding the grouping of claims rejected under 35 U.S.C. §102 in view of Kwoh et al., WO 96/39168. In the Appeal Brief, Appellants were clear that appealed Claims 40, 41, 42, 43, 44, and 45 each recited a separate element not taught or disclosed by Kwoh et al. and therefore each claim was separately patentable. In addition, Appellants stated that multiply dependent claims 46, 48, 51, and 52 did stand or fall together based on the patentability of the base claims, i.e., Claims 40-45.

The Examiner states that Claims 40 and 41 do stand or fall together because, according to the Examiner,

> "Claim 41 is related to claim 40 because achieving a level of essentially 0μg if [sic, of] CETP per ml (claim 41) would reduce the CETP activity (claim 40) to below 20% of that of untreated mammal." (See, Examiner's Answer, p. 3).

While it may be true that a concentration of 0μg/ml of CETP would necessarily reduce the level of CETP activity in the blood to below 20%, the converse is not necessarily true, i.e., that achieving a level of CETP activity below 20% does not achieve a blood concentration of 0μg/ml of CETP. The two claims recite different levels of CETP activity being achieved according to the method of the invention, and it is possible that the Board may find the teaching of Kwoh applicable to Claim 40 but not to Claim 41. And Appellants have separately argued that the reference suggests neither level of CETP being achieved by the immunization procedure contemplated in the claims.

Appellants assert that the embodiments of Claims 40 and 41 are distinct and must be separately considered with respect to the Kwoh reference, and therefore the grouping of the claims set forth in Appellants' Brief is correct.

Also with respect to the grouping of the claims, the Examiner states,

> "[T]he increase in circulating HDL (claims 42-43) and the decrease in circulating LDL (claims 44-45) are functionally related to the activity of CETP. As stated in the summary of the invention . . . CETP mediates transfer of HDL to VLDL and LDL and also the reciprocal exchange of VLDL to HDL. High CETP activity has been correlates [sic] with decreased levels of HDL and increased levels of LDL." (See, Examiner's Answer, pg. 3).

Appellants reiterate that the subject matter of Claims 42, 43, 44, and 45 each recite a separate element that is not disclosed in Kwoh. While they are present in the same metabolic system, the fact remains that CETP, HDL-cholesterol, and LDL-cholesterol are distinct proteinaceous entities. And while the Examiner refers to Appellants' disclosure for the statement the levels of CETP activity, high HDL and low LDL may be correllated, a causal relationship between the activity of CETP and the

levels of HDL and LDL is not established by the prior art and is a relationship only supported by data such as that presented in Appellants' application (which, of course, may not be relied on by the Examiner to tie the appealed claims together). Therefore, Claims 42-45 each recite a separate element of the present invention in that each relates to either the modulation of a different protein or, if the same protein, to a method of modulating the level of that protein, but to a different degree of activity. For this reason, as stated in the Appeal Brief, Claims 40, 41, 42, 43, 44, and 45 contain elements that must be independently evaluated in view of the cited prior art, and those claims stand or fall independently, not together. Claims 46, 48, 51, and 52 are multiply dependent from any of Claims 40-45 and will stand or fall together on the patentability of the base claims.

35 U.S.C. §112, first paragraph - Enablement

The Examiner maintains that the present application lacks an enabling disclosure pursuant to 35 U.S.C. §112, first paragraph. Specifically, the Examiner's position is that the specification does not enable the claimed methods of administering to "any" mammal "any" non-endogenous CETP in an amount effective to reduce CETP activity in the blood to a level that is less than 20% as compared to the untreated mammal, to achieve an unexpectedly low level of circulating CETP, i.e., essentially 0μg CETP per milliliter of blood, or to achieve an anti-atherogenic lipoprotein profile in the blood wherein there is an unexpectedly high level of HDL-cholesterol or an unexpectedly low level of LDL-cholesterol circulating in the bloodstream. The Examiner further rejected as inadequately enabled Appellants' claimed method as applied to humans or as employing a preferred group of whole, non-endogenous CETP molecules. Finally, the Examiner rejected as not enabled Appellants' claimed methods wherein adjuvants are employed.

According to the Examiner,

> "Other than the specific polypeptides mentioned above for a method of inhibiting the endogenous CETP activity, the specification fails to provide any guidance as how to make and use *any* nonendogenous CETP for a method of modulating any endogenous CETP in a mammal . . . Given the indefinite number of undisclosed non-endogenous CETP protein[s], it is unpredictable which undisclosed non-endogenous CETP would be useful for a method of inhibiting any non-endogenous CETP activity associated with atherosclerosis." (See, Examiner's Answer, pp. 5-6).

However, Appellants' claims are not directed to CETP or to a method of selecting *any* non-endogenous CETP, rather, Appellants' claims are directed to a method of using *a* whole, non-endogenous CETP to modulate endogenous CETP activity or lipoprotein levels. Obtaining a whole, non-endogenous CETP is presumed by the claim, and recognition and selection of an appropriate

whole, non-endogenous CETP is asserted to be within the skill in the art. It is a new use of such proteins that is the subject of the invetion on appeal: Appellants have discovered and demonstrated that administering a whole, non-endogenous CETP to a mammal will elicit production of antibodies that react with the mammal's own, endogenous CETP resulting in: (1) an unexpectedly low level of circulating CETP molecules (essentially no detectable CETP per ml of blood plasma) or of CETP activity below 20% of the activity in an untreated mammal, or (2) an unexpectedly high level of blood cholesterol in the form of "good cholesterol", i.e., HDL-cholesterol greater than 90%, or as high as 100%, or (3) an unexpectedly low level of blood cholesterol in the form of "bad cholesterol", i.e., LDL-cholesterol less than 10%, or as low as, essentially, none.

In addition, the specification provides examples of achieving such measurable results according to Appellants' claimed methods using a well-known rabbit model, which, Appellants assert, is a model widely accepted by persons skilled in the art as indicative of results that can be expected when administering the same or similar composition to a human subject.

The Examiner considers the claims as overly broad and requiring undue experimentation because a person skilled in the art allegedly would be unable to predict whether a particular whole, non-endogenous CETP would work in the claimed invention. However, on the contrary, Appellants' teaching allows persons skilled in this art to predict that administration of whole, non-endogenous CETP will cause defined results in circulating CETP activity, HDL level, or LDL level, AND Appellants' specification shows the person skilled in the art exactly how to administer, monitor, and test for confirmation of such predicted results.

Nowhere has the Examiner provided any evidence that would indicate that one skilled in the art would doubt the truth of what Appellants have demonstrated, using an animal model for atherosclerosis that is well known and widely used by persons skilled in this art.

> "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of §112 *unless* there is some reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *Fiers v. Sugano*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993), citing *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). (emphasis in original).

Therefore, by the legal standard set forth in *Fiers*, the Examiner must clearly set forth WHY one skilled in the art would, after reading Appellants' specification, *doubt the objective truth* of Appellants' demonstrated results. In other words, the Examiner must provide a sound scientific basis

why one skilled in the art, following the teachings of the disclosure, would be unable to practice the claimed method of modulating CETP involving (1) administering a whole, non-endogenous CETP to a subject, and (2) determining what effect said non-endogenous CETP has on the level of endogenous CETP activity in that subject.

35 U.S.C. §112, first paragraph - Written Description

The Examiner maintains the rejection of Claims 40-48, 51, and 52, stating that the present specification fails to reasonably convey to the person skilled in the art that the inventors were in possession of the claimed invention at the time of filing, i.e., does not satisfy the written description requirement under 35 U.S.C. §112, first paragraph.

According to the Examiner,

> "With the exception of the specific CETP polypeptides mentioned above, there is insufficient written description about the structure associated with functions of *any* non-endogenous CETP wherein said endogenous CETP is *any* xenogeneic CETP, *any* allelic variant of any mammalian's endogenous CETP, *any* mammalianized non-endogenous CETP having one more [sic, one or more] amino acid altered by deletion, or substitution as to make the amino acid sequence more similar to the mammal's endogenous CETP for a method of modulating the level of endogenous active cholesteryl ester transfer protein associated with atherosclerosis." (See, Examiner's Answer, page 9). (emphasis in original).

Again, the Examiner is not following the accepted legal standard required for establishing a *prima facie* case for a rejection under 35 U.S.C. §112, first paragraph for lack of a written description.

According to the well-established standards for written description as set forth by the Federal Circuit,

> "The written description must communicate that which is needed to enable the skilled artisan to make and use the claimed invention." [1]
>
> * * *
>
> "The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." 935 F.2d at 1563, 19 USPQ2d at 1117. (emphasis in original).

[1] *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), *citing*, *Kennecot Corp. v. Kyocera Int'l, Inc.*, 835 F.2d 1419, 1421, 5 USPQ2d 1194, 1197 (Fed. Cir. 1987), *cert. denied*, 486 U.S. 1008 (1988).

Upon review of the current specification and claims, it is clear that the present application satisfies the "written description" requirement because the present specification clearly describes what is now claimed.

Appellants note that the appealed claims recite levels of CETP activity or HDL levels or LDL levels that are directly supported by working examples. In the present application, there is an actual reduction to practice of a treatment to reduce CETP activity, raise HDL above 90% to 100%, and to lower LDL to less than 10% to essentially none, using a whole, non-endogenous CETP as a vaccine according to the description. (See, Example 1, pp. 16-20 of the application). The whole rhuCETP used in the examples is identified using a "structural chemical formula", namely, a complete amino acid sequence (SEQ ID NO: 1). The use of the CETP of SEQ ID NO: 1 to lower CETP activity below 20%, to raise HDL-cholesterol above 90%, and to lower LDL-cholesterol below 10% is described in detail. (See, e.g., Example 1, and Figures 8 and 9). Thus, the specification contains a demonstration of possession of the invention as claimed using the legal standard set forth in *Vas-Cath*.

Accordingly, all of the recitations of the claims under examination have been described (in writing) with such particularity that a person skilled in the art would understand that the inventors were in possession of a full conception of every feature of the invention recited in the claims, and the written description requirement of 35. U.S.C. §112 has been fully met.

35 U.S.C. §102(a)

The Examiner has maintained the rejection of Claims 40-45, 47, 51, and 52 under 35 U.S.C. §102(a) as being anticipated by Kwoh et al., WO 96/39168.

Again, it is well-settled law and spelled out in the MPEP §2131 that,

> **TO ANTICIPATE A CLAIM, THE REFERENCE MUST TEACH EVERY ELEMENT OF THE CLAIM**

The Kwoh et al. reference describes a study of CETP activity wherein an 11-mer peptide having a sequence common in human and rabbit CETP is tested for the ability to generate autoantibodies in rabbit and to reduce the level of endogenous CETP activity. Kwoh et al. compares the effects of immunization with a toxoid-conjugated and non-conjugated peptide over the course of a 28-week period. According to Kwoh et al. the toxoid-conjugated peptide reduced the level of CETP activity in rabbits to a greater degree than the non-conjugated peptide.

Kwoh et al. do not show any results from using a whole, non-endogenous CETP as specified in Appellants' claims. Further, there are no results presented in Kwoh that anticipate or suggest the unexpected CETP activity, HDL-cholesterol levels, or LDL-cholesterol levels recited directly in the appealed claims.

Elements of Appellants' claims being totally absent from the Kwoh reference, there can be no question that there is no anticipation of the appealed claims by the teaching of the Kwoh publication within the meaning of 35 U.S.C. §102.

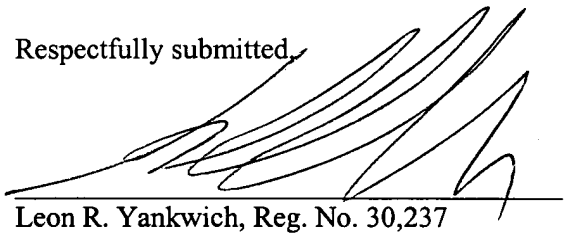
CONCLUSION

Appellants respectfully submit that the Examiner has failed to make out a *prima facie* case of lack of enablement or written description under 35 U.S.C. §112, first paragraph, or anticipation under 35 U.S.C. §102(a), against Appellants' methods.

The specification clearly describes the selection and administration of a whole, non-endogenous CETP as well as methods for determining changes in the levels of CETP activity and in the levels of circulating HDL- or LDL-cholesterol, which methods are not described in the prior art cited by the Examiner.

For all of the reasons set forth herein and in the previously submitted Brief on Appeal, the final rejections of Claims 40-48, 51, and 52 under 35 U.S.C. §112, first paragraph, and under 35 U.S.C. §102(a) as set forth in the final Office Action of September 10, 2002 are in error. Appellants respectfully request that each of the pending rejections be reversed by this Board and the present application passed to issue.

Respectfully submitted,



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CERTIFICATE OF MAILING

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March 2, 2004
date

Stephanie L. Leicht
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